DISCUSSION – ANTI-VEGF AGENTS

Dr. Lilenbaum: Dr. Wakelee, how much of an impact do you think the retrospective analysis in elderly patients had in your use of bevacizumab? Can we get a sense of how cautious we need to be?
Dr. Wakelee: When I have patients who are in their 70's and very fit, I still consider bevacizumab, and have proceeded in a couple of patients.
Dr. Lynch: I think the analysis was slightly underpowered to make a firm conclusion and Dr. Wakelee's interpretation that we should be cautious is absolutely accurate because, as you point out, the side effects appear to be higher.
Dr. Socinski: The older we get the more comorbidities we have, and this is not curative treatment. Bevacizumab is a good drug, but I think it's a toxic drug in certain patients, and so the risk has made me pause for patients over the age of 70. It does prolong survival but you don't want to have a discussion about improving survival and then have a first cycle grade IV or V event. You have not accomplished the prolonged survival if you exercise poor judgment with regard to patient selection.
Dr. Lynch: Is there any mechanistic reason why there should be a difference between men and women in terms of their benefit or lack of benefit from bevacizumab?
Dr. Heymach: We don't have the answer yet. We saw a gender difference favoring females in ECOG4599 and also in the two trials of ZD6474 with chemotherapy. One idea is that angiogenesis is more EGFR-dependent or the tumors are just more EGFR-dependent in females as compared to males. VEGF receptor levels are different between the genders. We're looking into whether estrogen receptor differences are driving the differences in angiogenesis.
Dr. Lynch: Dr. Wakelee showed us data that suggested in the AVAiL trial that both 7.5 mg/kg and 15 mg/kg every three weeks appeared to be efficacious. Any thoughts about dose of this drug and what we should be thinking about as we go forward?
Dr. Jain: I would speculate that if an anti-avascular effect were the key mechanism for bevacizumab efficacy, that a higher dose would be better. So to me the AVAiL trial data suggest that vascular normalization is probably the key mechanism. Otherwise one would get better response with a higher dose of bevacizumab.
Dr. Lynch: The expectation for sunitinib was that continuous dosing would be better, but the data is certainly suggesting that's not the case. Do you interpret this to mean it's not an anti-angiogenic mechanism, that it's more direct anti-tumor cell effects?
Dr. Heymach: I don't know how to interpret this data. We all know from the biomarker data that you can rebound from this agent relatively quickly. I think we have to be very careful in drawing conclusions from this, because this is not a randomized trial.
Dr. Socinski: But it does raise a lot of discomfort with what strategy should move forward.
Dr. Lynch: If you give bevacizumab it reduces blood vessel density about 50-percent after a single dose in rectal carcinoma patients, but if you look at FDG levels they do not change. On the other hand, if you give sunitinib, you begin to see a drop in FDG. Now FDG tells you more about cancer cells.
Dr. Socinski: Yes. But I'm not aware of any randomized trials that are being designed to address this issue.
Dr. Lynch: Do we have ways of predicting who is responding to anti-angiogenic agents? And what are your thoughts on how one can select patients who may benefit from these agents, and where are we now?
Dr. Heymach: No, not yet. What you're talking about is markers that predict, say, where you're going to have more benefit in chemotherapy plus bevacizumab as compared to just chemotherapy. A lot of the markers now being evaluated are inflammatory markers. We're casting a wide net and looking for predictive markers, because they're not going to be obvious. It looks as though having profiles or signatures of clusters of these cytokines together may be more predictive than individual markers.
Dr. Lynch: From an imaging standpoint do you think we have any way of figuring out who benefits from sorafenib or bevacizumab?
Dr. Sorensen: I think the best we can do is see early responders, so we can see in a week whether they're responding. But I don't know if we have any way for assessing this at baseline.
Dr. Lynch: How about PET, MRI or CT in helping us select patients? Are any of these close to allowing us to be able to select patients who might benefit from anti-angiogenic therapy?
Dr. Jain: I think we don't have an answer to that question in any cancers where anti-angiogenic agents have shown promise or have been approved. I think we will need an integrated approach of imaging combined with circulating markers.
Dr. Lynch: Dr. Janne, looking at it from the standpoint of someone who's helped to develop markers that are important in EGFR biology, what are your thoughts on the direction you're hearing about in VEGF therapy?
Dr. Janne: I don't think we have much at the moment in terms of pretreatment selection, which is where there are markers for EGFR based therapies. There are obviously some hints based on the radiographic changes but everyone has to be treated at that point. So I think there's a ways to go, and it's an active need, because one would assume that these agents may not work the same in all individuals.
Dr Lynch: I've heard some oncologists say that a predictive biomarker would have to be nearly 100-percent accurate, because they never want to refuse the opportunity for a patient to benefit from a drug.
Dr. Hirsch: The percentage of accuracy can be discussed, but I think that if we want to come close to that, we most likely need to find a combination of predictive biomarkers. I think

at the end of the day we need to find a paradigm with combination.

Dr. Lynch: But the argument is if you have a 20-percent chance of responding, which cancer patient wouldn't take that 20-percent chance?

Dr. Hirsch: I think you are right. But talking about VEGF inhibitors, we don't have any biomarker close to those numbers you are mentioning. And personally, I think we need to look into combinations of biomarkers.

Dr. Socinski: The question for these dual inhibitors is whether there is a difference in the toxicity - do they have the same risk as bevacizumab?

Dr. Engelman: Just to play devil's advocate, do you have any concern that they're actually not inhibiting angiogenesis in the patient and that's why there's no bleeding?

Dr. Socinski: Of course. Another possibility is that it's just a very weak VEGFR inhibitor and maybe that's why we're not getting any bleeding problems in squamous.

Dr. Shepherd: I really wonder whether this is both a weak VEGF-R and a weak EGFR inhibitor. We have had experience with it in various tumour types and I do not remember any patients developing a cavitary lesion, whereas with all the other VEGF inhibitors, 3- or 6- weeks later, cavitary lesions are usually seen in responding patients. I question the rationale of moving this drug forward as opposed to maybe putting two drugs that are stronger EGFR and stronger VEGF inhibitors together.

Dr. Lynch: Despite the fact that everybody thinks erlotinib is a better EGFR inhibitor and that 2171 is a better VEGF inhibitor, you've got to give 6474 credit for passing its randomized phase 2 test, and actually meeting the endpoints in these progression free survival trials.

Dr. Shepherd: The maintenance trial in small cell lung cancer performed by the National Cancer Institute of Canada Clinical Trials Group was negative.

Dr. Socinski: It may not be inhibiting angiogenesis. It may have benefits that have nothing to do with inhibiting angiogenesis.

Dr. Heymach: I believe it's a moderate VEGF inhibitor. By IC50s and other criteria, it's more potent than the first generation agents like 5416 and probably more than PTK787. In terms of VEGF inhibition, the two markers that have modulated significantly were a rise in VEGF and a drop in cycle VEGF-R2, which is taken as evidence of VEGF pathway inhibition as monotherapy. When we looked at the change in soluble VEGF-R2, after 21 days it caused about a 10-percent to 15-percent decrease in soluble VEGF-R2. Sunitinib, by contrast, after a week, causes about a 40-percent drop in VEGF-R2 and so does 2171.

Dr. Lynch: Can you comment on some of the difficulties with squamous cell? Do you think the histology's going to matter for the small molecules as well?

Dr. Wakelee: Yes. How much is a difficult question. We were part of ECOG 2501, which is a randomized discontinuation trial with sorafenib that included over 300 patients, over 20 of whom I treated personally. Two of my patients on this trial died from hemoptysis and both had squamous cell histology. They were both patients I wouldn't have treated with bevacizumab, but given the data, I felt that it was reasonable to put them on this study. Autopsies showed that both had tumor erosion through vessels, which the drug may have contributed to. We don't understand why squamous cell tumors tend to bleed, though the tendency to cavitate may play a role. We need to better understand exactly what causes the increased bleeding risk, because some squamous cell patients are fine with bevacizumab or small molecules, and some patients with adenocarcinoma aren't fine with either of these types of drugs. So although that's the best marker we have right now, it's probably not the true marker of bleeding risk. We do have to be cautious.

Dr. Lilenbaum: I agree. Now as we move away from a histology-based classification to a molecular-based classification, we'll be able to understand the different types of squamous and why some do bleed and others don't. But with what we have today I do think squamous histology is important.

Dr. Lynch: And would you treat a squamous patient off protocol with either sunitinib or sorafenib?

Dr. Lilenbaum: Not at this point.

Dr. Lynch: Would you put them on a protocol with sunitinib or sorafenib?

Dr. Lilenbaum: Yes.

Dr. Hirsch: I think in the future we'll face the question of histology much more than we ever have since we started to distinguish small cell and non-small cell. There are several studies pointing out that there is a difference in clinical course and response for adenocarcinoma and nonadenocarcinomas, so I think there will be much more demand for an exact histologic classification than we have seen before.

Dr. Socinski: I think that's definitely true, but on the other hand I think histology is probably the tip of the iceberg. Different pathways are probably operative in different degrees comparing squamous cell with adenocarcinomas.

Dr. Lynch: As we look at the twelve major trials prior to 4599 combining chemotherapy with other novel targeted drugs, it appears that most combinations were put together empirically. And so the question is, how should we be approaching these combinations more rationally? And particularly with a drug that we think may be working in antiangiogenic settings, do cell line based screens help you with drugs like bevacizumab, sunitinib and sorafenib?

Dr. Engelman: Unfortunately, I think Phase 1 work is really necessary to fully define toxicity of these combinations. Beyond Phase 1 is the major question. As soon as we begin to do all these Phase 1 trials, then are we also committed to randomized Phase 2 and 3 work, which is ultimately very expensive? I think that understanding the mechanisms by which a drug like bevacizumab might interact with chemotherapy overall may be important, but how much this can go beyond Phase 1, I think, is unclear.

Dr. Lynch: What are the best preclinical models? So thinking about how you put combinations together, you have empiricism, which is what has ruled the day so far, you've got cell line based screens where you take cell lines and treat them with different combinations and look for synergy, and finally you have murine models- both xenografts and genet-

ically engineered mice. Now for antiangiogenic drugs my impression is you're really limited to one of the two murine models if you really want to do this prospectively. Is that true?

Dr. Jain: Yes, you are limited to murine models, but for anti-angiogenic therapy I think the murine models have provided very nice insight. Actually all of the work on normalization was in mice before we saw it in rectal carcinoma patients. Your choice of animal models is very important, and they have to be transgenic or knockouts. I think just garden variety transplanted tumors are good if you are using proper doses in the appropriate animal models.

Dr. Hanke: I think the various mouse models have been useful for testing anti-angiogenic drugs and rational combination therapies. One of the problems with the murine models though is that they do not reflect the complexity of human tumor biology. This is somewhat less of a problem for anti-angiogenic drugs, as we are targeting host factors. However, the tumor will influence the stromal environment, so while positive results in mice is encouraging, they do not mean the agent will work in a particular human tumor.

Dr. Lynch: Dr. Hanke, from the perspective of someone who runs a large science endeavor for a pharmaceutical company, when you're thinking about putting drugs together and looking for combination or synergistic activity, what do you think, particularly if angiogenesis is a target, what are your perspectives on how one can best model that preclinically?

Dr. Hanke: We have to devise models to specifically address a particular hypothesis. So we can't just go into any standard xenograft or orthotopic model and expect the results to translate into man. There are probably 20 or 30 factors important in the angiogenesis cascade, and there can be a unique hierarchy to this in different tumors. Once we better understand the specific drives in a particular tumor, we can then do a good job to model the biology of that disease for a specific agent.

